Knowledge Acquisition Session Report

Session Date: September 11, 2003 **Session Time:** 4:30pm EST

Session Topic: User Requirements for a Clinical Trials Outcomes System

Knowledge Analyst: Jennifer Brush, ScenPro, Inc.

Session Location: DCP Offices, Rockville, MD

Type of Session:

__ Interview	__ Task Analysis	__ Scenario Analysis
__ Concept Analysis	__ Observation	_X_ Structured Interview

General Topic Area

The NCI Center for BioInformatics (NCICB) is funding an effort to develop a technical solution to the problem of providing complete and reliable clinical trial outcomes data to the cancer research community. Due to the large overall scope of developing a solution to collect, manage, report, and analyze clinical trial outcomes data, the project has been divided into multiple phases. The focus of this Phase I effort is on gathering specific user data requirements and desired system functionality.

Report Overview

This report documents information gathered during a Knowledge Acquisition session with members of the Division of Cancer Prevention, Gastrointestinal & Other Cancer Research Group (GOCRG). Dr. Ernest Hawk is the Chief Medical Officer of the GOCRG. Dr. Hawk's areas of responsibility include designing, conducting, and overseeing cancer prevention trials. Dr. Asad Umar is a Program Director within the GOCRG. Dr. Umar has expertise in the area of prevention trial biomarkers.

The GOCRG designs, develops, implements and monitors gastrointestinal and other cancer prevention research efforts. The GOCRG focuses on the areas of chemoprevention, nutrition, pharmacologic, biologic, genetic, vaccines or immunologic interventions for screening and early detection of cancer.

Summary Findings

Information obtained during this session includes:

- Differences in study design and results data collected across phases of prevention trials
- Sources, formats and types of results data associated with prevention trials
- Key characteristics of prevention trial outcomes that promote moving to the next research phase
- Current mechanisms and challenges associated with data integrity

Differences in Prevention Trial Design

Prevention trials are categorized into Phase I, Phase IIA, Phase IIB, and Phase III. The majority of GOCRG's trials are Phase II and III, but they have a few Phase I trials as well. Table 1.0 contains examples of the differences between study design characteristics for all prevention trial phases.

Trial Phase	Phase I	Phase II A	Phase II B	Phase III
Target Accrual	50	50	100-200	1,000 or more
Duration	6 months-1 year	6 months-1 year	6 months-1 year	1 year -5 years
Goals	• Establish drug pharmacokinetics - Absorption - Distribution - Metabolism - Excretion • Determine drug concentration levels in the blood • Dose findings	• Determine the biologic effect of drug on body/organ without toxic side effects	• Achieve biologic effect, short of cancer incidents (biomarker)	• Suppress development of disease • 100% reduction in lesion
Agent Administration	• Administer drug (no placebo) at several dose levels	• Administer drug (no placebo)	• Administer drug at 1 or 2 dose levels • Administer placebo	• Administer drug at 2 dose levels • Administer placebo
Endpoints	• Any biologic effect on cancerous tissue - Modulate proliferation of a tissue - Induce apoptosis	• Any biologic effect on cancerous tissue - Modulate proliferation of a tissue - Induce apoptosis	• Regression of a pre-cancer • Modulation/ change in pre-cancerous lesions	• Reduction in adenoma instance

Table 1.0 Differences in Prevention Trial Designs

The goals and study designs of Phase I and IIA are very similar: biologic information is gathered and analyzed to determine drug efficacy without a toxic effect. Phase IIB trials have similar endpoints to IIA, however IIB trials generally have a placebo and are conducted with a slightly larger cohort. Phase III trials involve more participants, multiple study arms and span a longer period of time.

Differences in Prevention Trial Results Data

As trial phases progress from Phase I and IIA through Phase IIB and III, the number and type of available results data increases, along with the number of study subjects. Table 2.0 includes examples of the different biological samples taken, tests administered, and results data collected during prevention trials.

Trial Phase	I	IIA	IIB	III
Samples Taken	• Blood (White & Red Cells) • Urine	• Blood (White & Red Cells) • Urine	• Blood (White & Red Cells) • Tissue Biopsy • Sputum • Serum	• Blood (White & Red Cells) • Tissue Biopsy • Sputum • Serum • Pancreatic Fluid • Stool
Tests / Results	• Blood Concentration Levels • Blood Interaction • Metabolites of Drug • Cellular (diseased vs. normal) - Proliferation - Apoptosis	• Blood Concentration Levels • Blood Interaction • Metabolites of Drug • Cellular (diseased vs. normal) - Proliferation - Apoptosis	• Observation - Measure lesions for multiplicity, size, incidence of new, change in size - Change in cancer size • Endoscopy • Cellular (diseased vs. normal) - Proliferation - Apoptosis	• Observation - Measure lesions for multiplicity, size, incidence of new, change in size - Change in cancer size • Endoscopy • Colonoscopy • Cellular (diseased vs. normal) - Proliferation - Apoptosis - Proteomic chip analysis • Molecular - Mutation assessment - Methylation - Epigenetic differences in tissue - Biochemical markers - Enzyme (changes) - Protein (changes)

Table 2.0 Differences in Results Data across Prevention Trial Phases

Prevention Trial Data Sources

Researchers and scientists obtain prevention trial data from a number of sources. These sources are illustrated in the figure below.

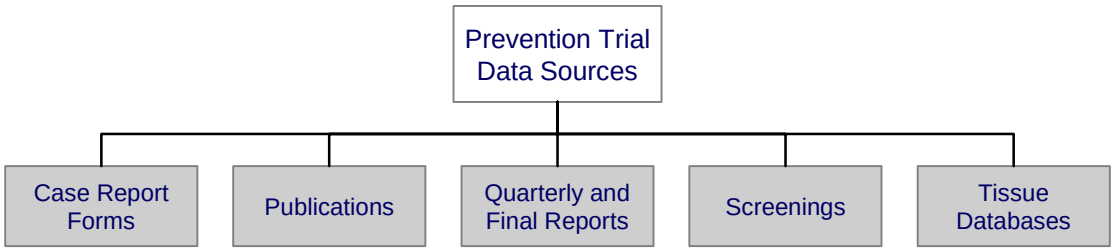


Figure 1.0 Prevention Trial Data Sources

Prevention Trial Data Formats

Outcomes data are produced from prevention trials are stored in multiple formats. The figure below illustrates a few of these stored outcomes formats.

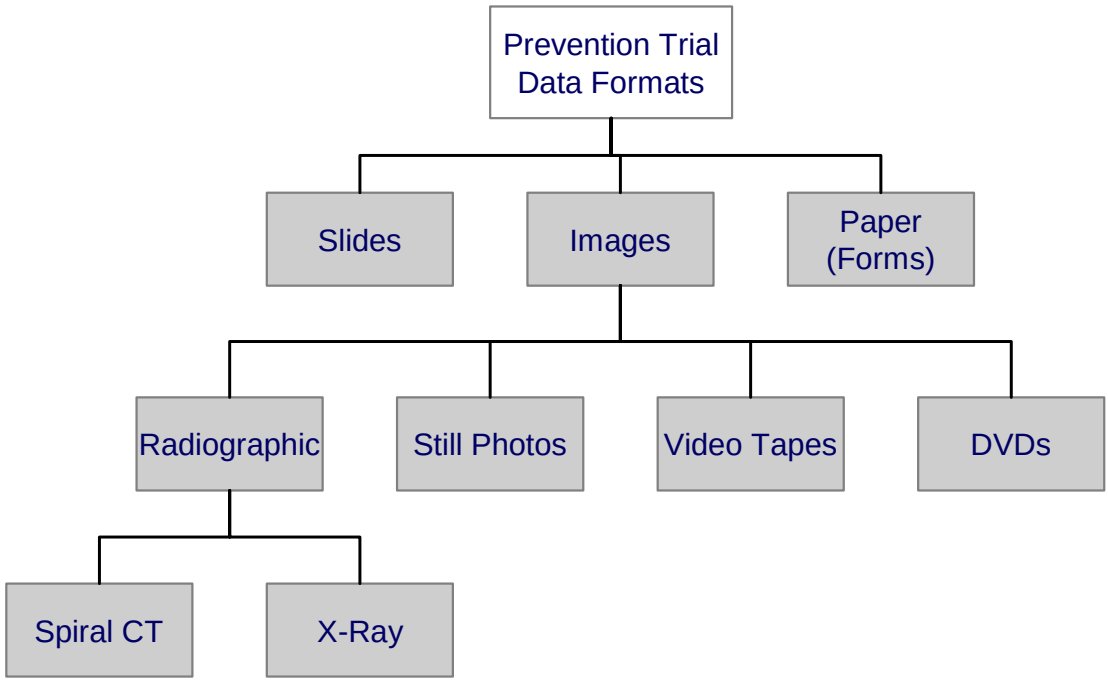


Figure 2.0 Prevention Trial Data Formats

Case Report Form Categories

Case Report Forms (CRFs) are source documents for patient encountered data on clinical prevention trials. These templates contain the required data content and format to be collected during studies. General CRFs are used for every study and contain similar information gathered at various points across each study. A study-specific CRF contains information that is dependant on the type of study being conducted. Pharmacokinetic forms are used mainly in Phase I trials to record the serum agent levels for pharmacokinetic analyses. Biomarker forms are used mainly in Phase II studies with biomarker endpoints to document results of biomarker assays. The purpose of the Schedule of Forms is to create an "at-a-glance" guide that identifies which forms are to be completed at various points within a study.

The figure below represents the various categories of Case Report Forms that are used in DCP prevention trials.

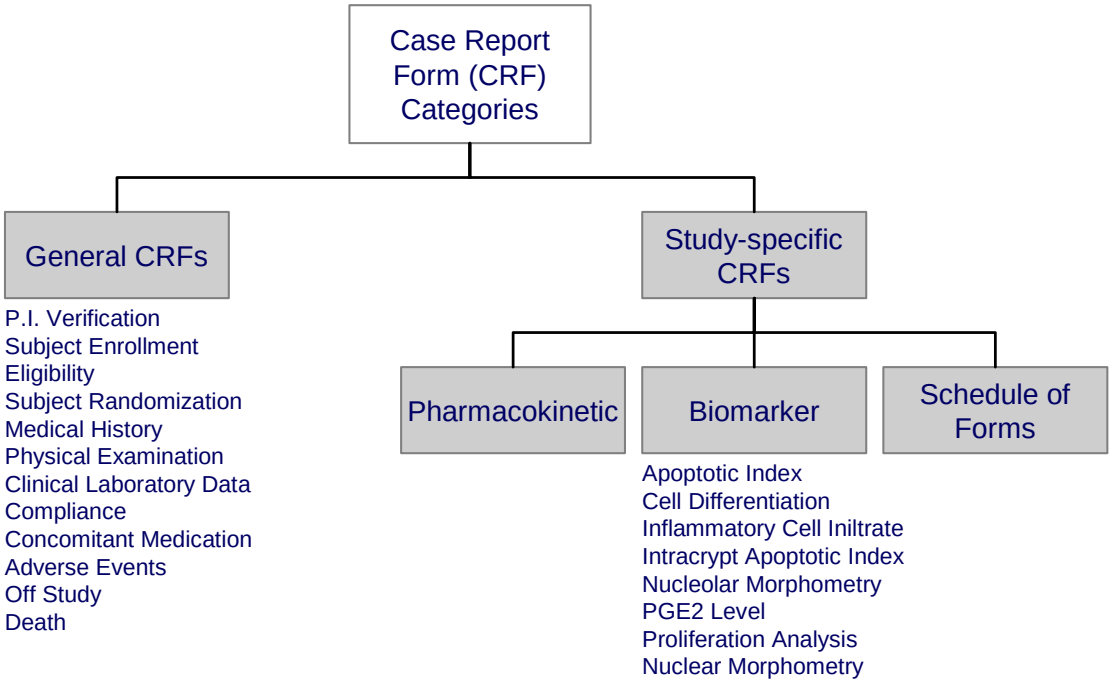


Figure 3.0 Case Report Form Categories

Key Characteristics of Prevention Outcomes that Promote Moving to the Next Prevention Research Phase

Prevention is a relatively new field in the cancer research spectrum. There are literally millions of unanswered questions about agents or other therapies that have the potential to prevent cancer incidence. As a result, prevention researchers are interested in collecting as much of this data as possible. Collecting large data sets provides researchers with the material needed to identify data characteristics that promote moving to the next trial phase. Table 3.0 is a comparison of a Phase II and Phase III trial. The components of each trial and the characteristics that trigger a move into the next research phase are described in detail below.

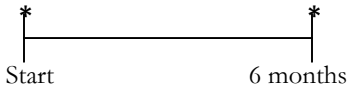
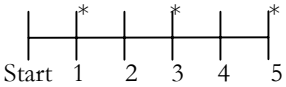
Trial Phase	Phase II	Phase III
Target Accrual	85	2,000
Study Design	• Administer drug at 2 dose levels • Administer placebo	• Administer drug at 2 dose levels • Administer placebo • Study Arms - Arm 1: Take drug earlier in the disease - Arm 2: Combination drug with same Phase II protocol - Arm 3: Taking Phase II drug into a different cohort
Duration	6 months	1 year -5 years
Eligibility Criteria	Polyps or adenomas at entry of trial	Past adenoma (none currently)
Endpoint	Regression of polyps or adenomas	Reduction in adenoma instance
Assessment Method	Review of video endoscopy by experts	Interval video colonoscopies
Assessment Parameter	(A) # of polyps (B) size of polyps (A) X (B) = Polyp Burden (C)	(A) # of polyps (B) size of polyps (A) X (B) = Polyp Burden (C)
Assessment Frequency	• Start of trial • End of trial 	• Year 1 • Year 3 • Year 5 
Outcome	30% reduction in number of polyps (A), 35% reduction in overall burden of polyps (C)	100% reduction in number of polyps (A)

Table 3.0 Moving from a Phase II to Phase III Prevention Trial

Study Design and Eligibility Criteria

Participants in the Phase II trial all had polyps. This hard, quantitative endpoint made it possible to see definitive results in a short period of time. For this phase, there was a 30 to 35% reduction in polyp number and burden.

Phase II's positive results provide a trigger to move the same drug into a Phase III trial. Phase III trial participants do not have existing polyps. Their eligibility criteria include a previous incidence of having polyps. This criteria allows for a larger sample size, though the lack of a hard endpoint means

the trial will have a longer duration than the Phase II. One subset (arm) of the participant population is given the agent from Phase II in combination with a known effective agent. It is hoped that this will result in an increase in the effectiveness from 30% to near 100%.

Assessment
A video endoscopy of the duodenum and colon is taken at the start of the Phase II trial. Scientists review the videos and literally count and measure the diameter of each polyp for each participant. The polyp burden is calculated by multiplying the polyp total and diameters. This burden number becomes the hard endpoint. Following six months of treatment, each participant is assessed again using the same method. A 30% reduction in the number of polyps and a 35% reduction in the overall polyp burden is the result. This preliminary assessment reveals that the drug is active in that cohort and requires additional analyses.

Additional analyses are performed on the video endoscopies and tissue samples. These analyses include:

- systematic review of each video tape
- serum analysis from tissue samples
- performing proliferation and apoptosis rates on tissue samples (cellular level biomarker)
- molecular analysis of tissue samples
- identifying proteomic patterns of protein from serum
- determining drug effect markers by measuring enzymes at the protein level

The above analyses conclude that the drug is effective in regressing pre-cancerous lesions. This is the major incentive to move into a Phase III trial.

Data Integrity

The Division of Cancer Prevention (DCP) focuses on FDA requirements, drug development, and scientific accuracy in regards to data integrity. DCP utilizes an in-house monitoring system to assess the integrity of clinical data to be incorporated into DCP studies. Biomarker pathologic data is analyzed by two independent groups, the drug company and independent statisticians. Histological data is reviewed by certified pathologists in certified labs. Dr. Hawk recommended talking to someone from Early Detection Research Network (EDRN). EDRN is in the process of standardizing collection and reporting methods that are reproducible across labs.

One potential source of disparate data with questionable reliability or integrity is health care organizations outside the patient's assigned cancer center. For example, a patient may have an event which sends them to the local emergency room. During this patient encounter, data may be collected or submitted by a non-certified institution or individual. This data is important and contributes to the study, but may not be assessed for integrity and adds to the risk of inconsistent data.

When a patient participates in a large trial, it may be more convenient for them to have routine lab tests performed at a local lab rather than traveling to the primary cancer center. There is no standard set for collecting, transferring or receiving that data.

Linking Data across Trials

DCP has instituted measures to address patient data de-identification to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). DCP has identified data elements that must be omitted in order to comply with HIPAA issues when patient data is reported. However, this data omission practice frequently results in the inability to link participant data across trials.

Roles and Responsibilities of Individuals involved in Prevention Trials

Role	Responsibility
Study Principal Investigator	The individual responsible for the conduct of the study at the clinical center and for ensuring the safety of study participants enrolled at that site.
Contract/Grant Principal Investigator	Has organizational and fiscal responsibility for the use of Federal funds to conduct a clinical study or cooperative agreement as stated on the funding document.
Site Coordinator	Individual responsible for the local management of Phase II and III chemoprevention clinical trials conducted through a contract mechanism with DCP.
NCI Contractor Officer	Contractor officer as stated in the contract award document.
NCI Procurement Technician	Additional KA required.
Medical Monitor	Doctor responsible for monitoring the entire life of a protocol.
Project Officer	Provides scientific and technical oversight of contract projects.
Program Director	Provides scientific and technical oversight of grants and cooperative agreements.
DCP Nurse Specialist	Serves as a resource and liaison to site staff, participates in the management of cancer prevention research protocols, and updates the PI on study status.

Wish List

DCP personnel believe that linking efficacy data across trials would be very valuable. Preventive agents could be identified that prevent cancer in multiple target organs. Therapeutic agents are being developed with fewer side effects so they can be used in low risk populations. Linking data across trials is valuable not just for cancer prevention and therapy, but for the potential impact on other chronic disease of aging including cardiovascular disease and osteoporosis.

Dr. Hawk stated the need for data validation and standardizing techniques to accomplish the goal of making today's biomarkers tomorrow's endpoint. Building systems to improve drug development, scientific accuracy and data integrity will help scientists reach that goal. As techniques, technology and science advance, Dr. Umar noted the need for the system to be flexible enough to keep up with the changing standards.

Entries for Domain Dictionary

Adenoma: A non-cancerous tumor.

Apoptosis: A normal series of events in a cell that leads to its death.

Biomarker: A diagnostic indication that disease may develop.

Drug Effect Marker: The effect of a drug or chemical on an organ, region, tissue or organism and the physiological and psychological processes associated with each.

Duodenum: The first part of the small intestine.

Endoscopy: The use of a thin, lighted tube (called an endoscope) to examine the inside of the body.

Epigenetic: Changes in the regulation of the expression of gene activity without alteration of genetic structure.

Methylation: The attachment of a methyl group to a molecule.

Pharmacokinetics: The activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted.

Placebo: An inactive substance that looks the same as, and is administered in the same way as, a drug in a clinical trial.

Proliferation: An increase in the number of cells as a result of cell growth and cell division.